Summary

The idea that saponifiable phospholipids are only building blocks and energy source of a cell has been refuted by the discovery of phospholipid signalling. Currently, these lipids are widely studied, mainly because of their potential undiscovered functions. One aspect that makes the study of phospholipids difficult, is their limited availability in pure form. Biological membranes, which are the main source of phospholipids, are typically composed of several tens to hundreds very similar species. In this mixture, only a minute amount of a single species might have a specific physiological property. To find, and to isolate this lipid reminds of the phrase "search the needle in a haystack". Despite organic chemistry cannot help finding the needle directly, it offers a different solution; to prepare a new needle. However, this requires efficient strategies that allow the synthesis of defined, chemically pure lipids and their derivatives. This is what this thesis presents.

Chapter 2 describes a modular synthesis of branched fatty acids, which are mainly lipid components of the membranes of various bacterial pathogens. The described synthesis allows preparation of a fatty acid bearing the methyl-branch at any position of the linear chain together with the desired absolute configuration.

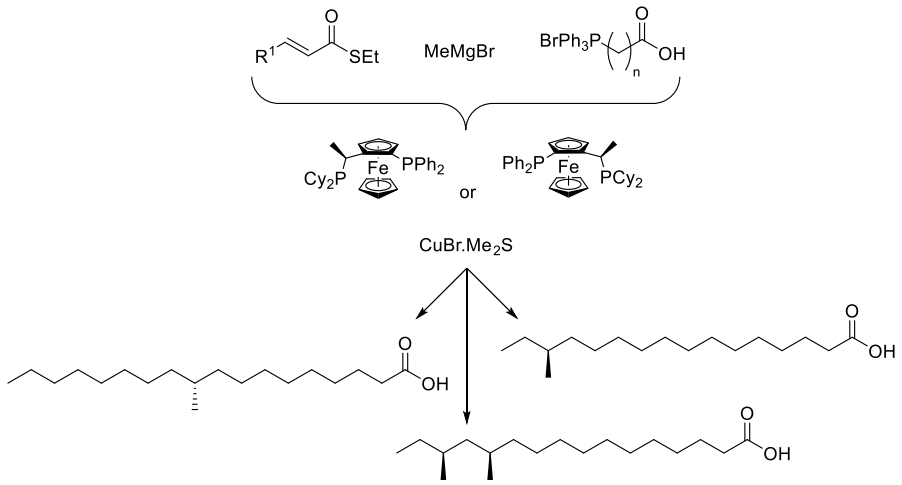

Figure 1. Modular synthesis of branched fatty acids.

This modular approach was successfully applied in the synthesis of 3 different fatty acids in the amounts relevant for further studies.

Despite the fact that glycerophospholipids seem relatively simple compounds, their synthesis might be surprisingly complex. Chapter 3 is devoted to the synthesis of these glycerophospholipids. A cobalt catalyst allowed the regioselective ring opening of a silyl protected glycidol. The obtained protected

monoacylglycerol was further esterified in the same pot. The resulting silyl protected diacylglycerol was deprotected without any notable migration, and subsequently converted to a phospholipid.

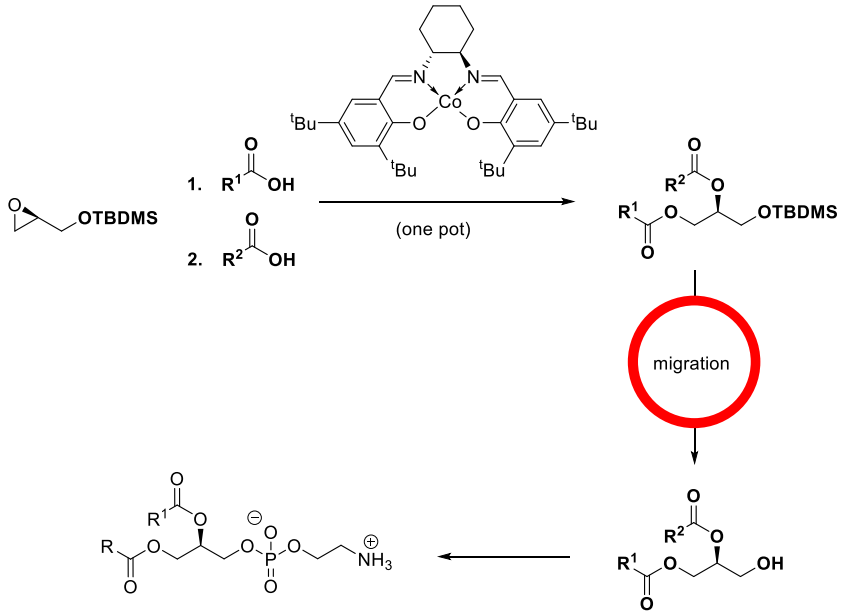

Figure 2. One pot synthesis of protected diacylglycerols and the subsequent conversion to a phospholipid.

Chapter 4 is an extension of this methodology to the synthesis of triacylglycerols. When glycidyl esters were used as the starting material, the same conditions afforded enantiopure triacylglycerols. This methodology was demonstrated in the synthesis of 18 different triacylglycerols.

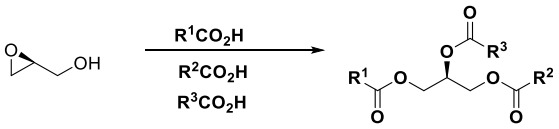

Figure 3. An efficient, 3 step synthesis of triacylglycerols.

Furthermore, this chapter described the first steps towards the automated synthesis of triacylglycerols by a liquid-handling platform. The obtained triacylglycerols can be applied as analytical standard in the analysis of triacylglycerols mixtures such as milk fat.

The synthetic solutions described in the chapters 2 and 3 allowed the synthesis of phospholipids bearing methyl branched fatty acids. These lipids were

prepared in amounts, which allowed initial studies of their properties as membrane components.

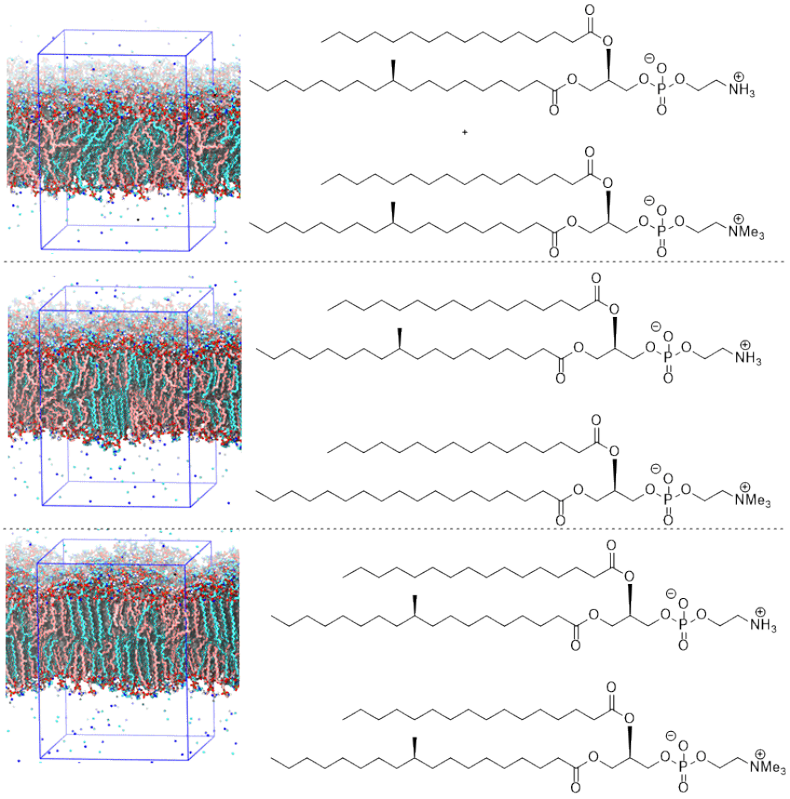

Figure 4. Study of the influence of a methyl-branch on the organization of a bilayer.

The phospholipids were converted into 2-component liposomes. The bilayers of these liposomes were studied by molecular dynamics simulations. Another studied aspect of these lipids was their interaction with membrane proteins.

Chapter 6 is also dedicated to the influence of lipids on protein function, but from a different perspective. Protein lipidation is a posttranslational modification, by which lipids control the activity of proteins. The chapter describes the synthesis of a lipid probe, which might be useful in protein lipidation studies in living cells.

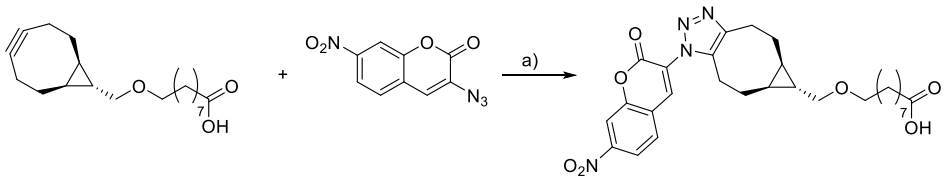

Figure 5. A probe for the study of protein lipidation displays a rapid and clean dipolar cycloaddition.

Chapter 7 is dedicated to (phospho)lipids found in Archaea. Archaea form a domain of Life, which early in evolution strayed from the remaining 2 domains.

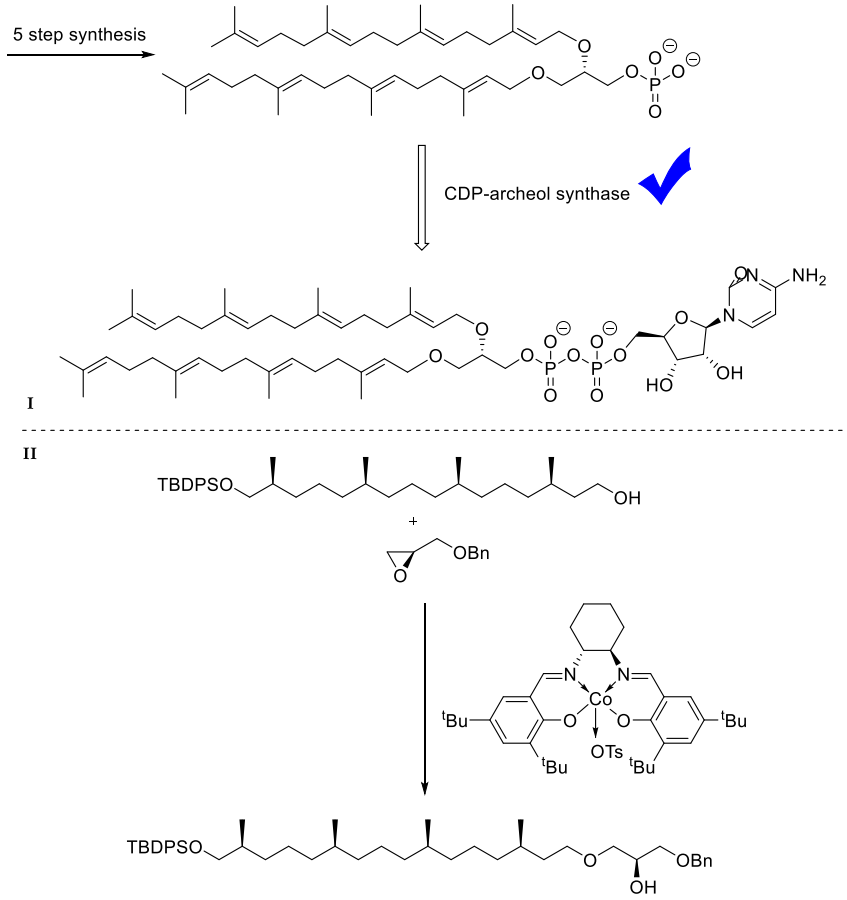

Figure 6. (I) Synthesis of a biosynthetic intermediate in archaeal lipid biosynthesis for the identification of an involved enzyme; (II) Epoxide ring opening as a key step in the total synthesis of cycloarchaeol.

The separated evolution granted, that the species from this domain developed their own lipid biosynthetic pathways. Study of these pathways is challenging because there are few assays and the corresponding biosynthetic intermediates are not available. Chapter 7 presents a synthesis of one of these intermediates, which was necessary for the identification of one of the missing enzymes in archaeal lipid biosynthesis. Furthermore, chapter 7 describes a key step in the total synthesis of cycloarchaeol – an archaeal lipid backbone.